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Risk of mortality among patients with epilepsy in southern Taiwan

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ABSTRACT

Objective: Previous studies suggested a higher risk of all-cause mortality in patients with epilepsy than in the general population. However, information on the age- and sex-specific risk of mortality, as well as on the cause-specific risk of mortality has been sparse. This study aims to determine sex-, age-, and cause-specific risk of mortality among patients with epilepsy from southern Taiwan.
Methods: A total of 2180 patients treated in a tertiary hospital in southern Taiwan between 1989 and 2008 were compared to the general population of Taiwan for age-, sex- and cause-specific mortalities. The age-, sex-, and calendar year-standardized mortality ratios (SMRs) were calculated to estimate the relative risks of mortality associated with the epilepsy.
Results: There are 266 (12.2%) deaths noted in the study period. The patients with epilepsy experienced a significantly increased SMR of all-cause mortality (SMR, 2.5; 95% confidence interval (CI), 2.2–2.8). The most significantly elevated age-specific SMR was 51.8 (95% CI, 6.2–187.2) and 8.6 (95% CI, 4.4–14.9) for male patients aged 0–9 years and female patients aged 20–29 years, respectively. Additionally, the most increased cause-specific SMR was noted for brain tumor (SMR, 21.4; 95% CI, 9.23–23.1), followed by accidental drowning (SMR, 8.8; 95% CI, 3.5–9.6) and falls (SMR, 5.7; 95% CI, 2.2–6.1).
Conclusion: Younger epilepsy should be the object of aggressive treatments. Advancement in treating brain tumors and prevention of accidental injuries may help improve the survival of patients with epilepsy.

1. Introduction

Mortality in people with epilepsy exceeds that in the general population,[1–5] which is especially true for certain causes of death including cerebrovascular disease (CVD),[2,3,6] neoplastic disorders,[2,3,6] pneumonia,[2,3] poisoning,[7] and suicide.[8–10] In a recent review, Neligan et al. examined the temporal trends in the mortality of people with epilepsy and noted that the standardized mortality ratio (SMR) of mortality is highest in the initial years after diagnosis[11]; and there is no evidence that either the overall SMR or the mortality rate of people with epilepsy has changed significantly over time. Compared to the general population, the SMR for all-cause deaths varied from 1.6 to 5.3,[12] and the variation in cause-specific SMRs is usually grater. Common causes of deaths were also observed in certain selected epilepsy populations where patients with frequent and severe seizures are more common, and the SMRs for these selected epilepsy populations are three to six fold higher compared to those noted in population-based studies.[7,13–18] Although an increased mortality risk of all accidents was also noted in patients with epilepsy,[2,7,14,19] information concerning risk of death from specific cause of accidental death, such as drowning[20] and driving fatalities[21] has been neither comprehensive nor consistent, mainly due to certain methodological problems including small sample size and employment of patients with varying frequency of seizures.

Despite that the excess mortality in people with epilepsy has been well documented in the literature, most of studies were conducted in European and North American nations.[12,13,22] While there were data on prevalence of epilepsy from some developing countries, there is little information on the mortality of epilepsy in these populations. Limited information concerning mortality from epilepsy was available in developing countries, which was mainly due to the fact that death certificates are usually unreliable and often unavailable, and the cause of death is difficult to determine in many developing countries.[23] Meanwhile, information on mortality risk associated with epilepsy has also been rarely reported in Asian nations including Taiwan.[24,25] A community-based survey of 13,663 subjects aged 30 years or older reported an active epilepsy prevalence of 3.8/1000 in Taiwan, and the lifetime prevalence rate

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of epilepsy (including active epilepsy and epilepsy in remission) was estimated at 3.14/1000 for age above 30 years. In comparison with prior surveys, the study also indicated that the prevalence rate of epilepsy was rather stable over the in recent two decades.[26] Concerning the mortality risk, there have been only two hospital-based studies carried out to investigate the risk of mortality in Taiwanese patients with epilepsy.[24,25] Due to small sample size, interpretation of cause-specific mortality risk is rather limited, and reliable mortality risk estimates for detailed age and sex stratifications were not likely. We therefore conducted this cohort study with a larger cohort of people with epilepsy recruited from a tertiary hospital in southern Taiwan. With a sufficient number of study subjects, this study aims to investigate the sex, age, and cause-specific mortality risk associated with epilepsy in Taiwan. Results from this study were also compared with findings from other nations globally.

2. Subjects and methods

Between 1989 and 2008, a total of 2180 prevalent epilepsy patients, including 1214 men and 966 women, were treated at a tertiary hospital in southern Taiwan. We reviewed medical charts of those patients for their demographic characteristics and clinical manifestations of the disease. The charts included personal identification number (PIN), gender, date of birth, and date of the initial diagnosis of epilepsy. Information on seizure type and diagnosis was ascertained according to the guidelines recommended by the Commission on Epidemiology and Prognosis of the International League against Epilepsy.[27]

The cohort was then linked, using PIN, to Taiwan Death Register (TDR) between 1989 and 2008. The TDR is considered accurate and complete because it is mandatory to register all deaths in Taiwan and for physicians to complete all death certificates.[28] The linkage showed that 266 patients died by the end of 2008. Information on date of death and underlying cause of death (UCOD) coded according to the International Classification of Diseases 9th or 10th Clinical Modification (ICD-9-CM for 1988–2007 and ICD-10-CM for 2008) were retrieved from the TDR.

We compared patients' risks of overall and age- and sex-specific mortality to those of the general population. We also compared the risks of mortality from various causes including malignant neoplasms (ICD codes: 140–208 & C00-C97), heart disease (ICD code: 398, 402, 416, 425, 427–428 & I09, I11, I27, I42, I49, I50), ischemic heart disease (ICD codes: 410–414 & I20-I25), cerebrovascular disease (ICD codes: 430–438 & I60-I69), pneumonia (ICD codes: 480–486 & J12-J18), liver cirrhosis (ICD codes: 571 & K70, K73-K74), and injury (ICD code: E800-E999 & V01-Y89) between the patients with epilepsy and the general population. The expected number of death for the epileptic cohort was calculated from the person-year approach, using the age (10-year intervals) and sex-specific annual mortality rates with reference to the general population. We first calculated the number of person-years being observed for each study subject. The date of study entry was the date of initial primary or secondary diagnosis as epilepsy during the study period, i.e., 1989–2008. The date of completion of follow-up was the date of death encountered by the study subjects who died prior to the end of 2008. For those who were intact during the study period, the date of end-of-follow-up was set to be December 31, 2008. The annual age-sex-specific population sizes for the general population during the study period were derived from the national annual household registration statistics published by Ministry of the Interior of Taiwan. Standardized mortality ratios (SMRs) were calculated as relative risk estimates. The average annual average size of the general population over the study period was 21,769,198. The 95% confidence interval (CI) for SMR was estimated using the exact estimation.[29,30] The analysis was performed using SAS (version 9.1; SAS Institute, Cary, NC), and level of significance was set at a p-value of 0.05. The National Cheng Kung University Medical School IRB has approval of this study (ER-98-065).

3. Results

The study cohort consisted of 1214 male subjects and 966 females. The age ranged from 0 to 82 years at the first appearance in the cooperative hospital, with a median and mean (±SD) age of 15 and 21 ± 16 years old, respectively. Over a maximum of nearly 20 years of follow-up, a total of 22,617 person-years were accumulated. The length of follow-up varied, ranging from 0 to 4 years (n = 423), 5 to 9 years (n = 601), 10 to 14 years (n = 664), and 15 years and longer (n = 492). Totally, 266 deaths (193 men and 73 women) were noted at the end of follow-up. The mean age at death was 50 years (SD = 19 years) for all 266 deceased subjects.

Table 1 shows the overall and age- and sex-specific SMRs of all-cause mortality. The overall SMR was significantly increased for patients with epilepsy (SMR, 2.5; 95% CI, 2.2–2.8). Both male and female patients had a very similar risk estimate. The age-specific SMR was also significantly increased in patients with epilepsy of all age groups except those aged 10–19 and 70+ years. The most elevated SMR was noted in young children epilepsy aged 0–9 (SMR, 34.0; 95% CI, 4.1–122.8) followed by those aged 20–29 years (SMR, 6.3; 95% CI, 4.4–8.7). The age-sex-specific analysis showed that the most increased SMR for male patients was noted in children patients aged 0–9 years (SMR, 51.8; 95% CI, 6.2–187.2) followed by those aged 20–29 years (SMR, 5.6; 95% CI, 3.5–8.2), while patients aged 20–29 years were at the most elevated risk of mortality (SMR, 8.6; 95% CI, 4.4–14.9) in females.

The cause-specific SMRs are shown in Table 2. The SMR of all malignant neoplasm was significantly increased at 1.7 (95% CI, 1.2–1.7). The cancer-specific analysis further indicated a substantially and significantly increased SMR for brain tumor (SMR, 21.4; 95% CI, 9.2–23.1). We also noted a significantly increased SMR for liver cancer (2.6; 95% CI, 1.4–2.7). In addition to malignant neoplasm, heart disease (SMR, 2.6; 95% CI, 1.2–2.7), cerebrovascular disease (SMR, 2.6; 95% CI, 1.6–2.6) and pneumonia (SMR, 2.5; 95% CI, 1.1–2.7) were all significantly and positively associated with epilepsy mortality. On the other hand, we found no significant association of epilepsy with mortality from ischemic heart disease or liver cirrhosis. Patients with epilepsy were also at a significantly increased SMR for all injuries (SMR, 3.6; 95% CI, 2.7–3.6), as well as for certain injuries including transport accidents (SMR, 2.5; 95% CI, 1.4–2.6), accidental falls (SMR, 5.7; 95% CI, 2.2–6.1), accidental drowning (SMR, 8.8; 95% CI, 3.5–9.6), and suicide (SMR, 4.0; 95% CI, 2.4–4.1).

4. Discussion

4.1. Main findings

In 22,617 person-years observed over nearly 20 years, we noted an SMR of 2.5 for all-cause mortality in our sample patients, with a slightly higher risk estimate for men (SMR = 2.6) than for women (SMR = 2.2). In the age-specific analysis, our study noted a remarkably increased risk of mortality in younger patients with epilepsy. Like findings from the studies of many developed nations, our study also noted that Taiwanese people with epilepsy were also at significantly elevated risk of mortality from non-injury causes including malignant neoplasm (especially form brain tumor), cerebrovascular disease, pneumonia, and suicide, with an SMR ranging from 1.7 for malignant neoplasm (21.4 for brain tumor) to 2.6 for cerebrovascular disease. Additionally, SMRs for certain injury related causes, such as drowning (8.8) and fall (5.7)

Table 1
Standardized mortality ratio (SMR) for patients with epilepsy.

Age (year)	Sex	No. of patients	No. of person-years	No. of deaths		SMR[a]	95% CI
				Observed	Expected		
0–9	Male	54	104	2	0.04	51.8	6.2–187.2
	Female	33	71	0	0.02	–	
	Total	87	174	2	0.06	34.0	4.1–122.8
10–19	Male	293	1251	2	0.77	2.6	0.3–9.4
	Female	223	923	0	0.27	0.0	0–13.7
	Total	516	2173	2	1.04	1.9	0.2–6.9
20–29	Male	338	3690	24	4.32	5.6	3.5–8.2
	Female	313	2962	12	1.40	8.6	4.4–14.9
	Total	651	6652	36	5.72	6.3	4.4–8.7
30–39	Male	208	2954	35	6.45	5.4	3.7–7.5
	Female	175	2637	10	2.10	4.8	2.2–8.7
	Total	383	5590	45	8.55	5.3	3.8–7.0
40–49	Male	159	2158	38	9.46	4.0	2.8–5.5
	Female	111	1776	13	2.97	4.4	2.3–7.4
	Total	270	3934	51	12.43	4.1	3.0–5.3
50–59	Male	65	1260	31	10.74	2.9	1.9–4.0
	Female	50	965	7	3.70	1.9	0.7–3.8
	Total	115	2225	38	14.44	2.6	1.8–3.6
60–69	Male	54	555	22	10.62	2.1	1.2–3.1
	Female	39	420	10	4.47	2.2	1.0–4.1
	Total	93	975	32	15.08	2.1	1.4–2.9
70+	Male	39	525	39	31.10	1.3	0.8–1.7
	Female	20	369	21	17.73	1.2	0.7–1.8
	Total	59	893	60	48.83	1.2	0.9–1.5
All	Male	1214	12,495	193	73.48	2.6	2.2–3.0
	Female	966	10,121	73	32.67	2.2	1.7–2.8
	Total	2180	22,617	266	106.15	2.5	2.2–2.8

CI, confidence interval.
[a] Overall SMR was standardized for age, sex, and calendar year; age-specific SMR was standardized for sex and calendar year; sex-specific SMR was standardized for age and calendar year; age-sex-specific SMR was standardized for calendar year.

were substantially high in patients with epilepsy. Our results also provided support for an increased risk of mortality from suicide and transport accidents in patients with epilepsy, with an SMR of 4.0 and 2.5, respectively. Given that the SMRs for all-cause mortality ranged from 1.6 to 5.3 in most previous community-based studies, and tended to be higher in studies of selected population (3.2–7.9),[12] the patients with epilepsy in southern Taiwan experienced essentially the same magnitude of increased risk of mortality, as compared to the general Taiwanese population.

4.2. Age and sex-specific SMR

Although highest in the younger patients, the SMR was significantly increased in all age groups before 70 years. Like many previous studies,[7,13] our study also found an inverse relation

Table 2
Cause-specific standardized mortality ratio (SMR) in patients with epilepsy.

Cause of death (ICD-9-CM code & ICD-10-CM)	No. of deaths		SMR	95% CI
	Observed	Expected		
Malignant neoplasm (140–208 & C00-C97)	48	28.1	1.7	1.2–1.7
Malignant neoplasm of liver (155 & C22)	15	5.8	2.6	1.4–2.7
Malignant neoplasm of lung (162 & C34)	6	5.2	1.1	0.4–1.2
Brain tumor (191& C71)	8	0.4	21.4	9.2–23.1
Malignant neoplasm except brain tumor (140–208, excluding191 & C00-C97 excluding C71)	40	27.7	1.4	1.0–1.4
Heart disease (398, 402, 416, 425, 427–428 & I09, I11, I27, I42, I49, I50)	10	3.9	2.6	1.2–2.7
Ischemic heart disease (410–414 & I20-I25)	4	4.9	0.8	0.2–0.9
Cerebrovascular disease (430–438 & I60-I69)	25	9.8	2.6	1.6–2.6
Pneumonia (480–486 & J12-18)	9	3.6	2.5	1.1–2.7
Liver cirrhosis (571 & K70, K73-K74)	10	4.9	2.1	0.9–2.1
Accidents and injury (E800-E999 & V01-Y89)	55	15.2	3.6	2.7–3.6
Motor vehicle traffic accident (E800-E848 & V01-V99)	15	6.0	2.5	1.4–2.6
Accidental falls (E880–E888 & W00-W19)	7	1.2	5.7	2.2–6.1
Accidental drowning (E910& W65-W74)	7	0.8	8.8	3.5–9.6
Suicide (E950-E959 & X60-X84)	14	3.5	4.0	2.1–4.1

CI, confidence interval.

between SMR and age. The highest SMRs were found in children, while decreasing SMRs were found with increasing age. A recent study reported that childhood-onset epilepsy was associated with a substantially higher risk of epilepsy-related death, including sudden and unexplained death.[31] The study by Sillanpää et al. also noted that younger patients with epilepsy had a greater risk of mortality from suicide.[31] Previous studies noted that the risk of suicide is even greater in epilepsy youth with depression,[32] and the prevalence of depression and anxiety in children and adolescents with epilepsy was considered high.[33] Moreover, previous studies reported that young people with epilepsy tended to have poor compliance with antiepileptic treatment and adopt behaviors that could increase their risk of mortality from epilepsy, for example, using alcohol and recreational drugs that may lower their seizure threshold.[34] Alternatively, the high SMR in children and young adults with epilepsy could simply be a reflection of both the low mortality in the reference population and high mortality in patients suffering from epilepsy.[35,36] We further examined the UCOD for the two boys (<10 years) who died in our study. The two boys died of septicemia (ICD-9: 038) at 5 years old and epilepsy and recurrent seizures (ICD-9: 345) at age of 8, respectively. Based on such small numbers of death and person-years observed in this age category, we were unable to look into the possible causes for the substantially increased SMR in young children. Meanwhile, we could not exclude the possibility that the substantially high SMR noted in young children was due to random variation in risk estimates, represented by a wide confidence interval of SMR.

Most studies[1,2,4,6] observed a higher mortality risk in epilepsy males than in their female counterparts. However, compared to the general population of the same gender, our data showed only small difference in sex-specific SMR for adult patients, but still presented some variations in sex-specific SMR for children and young adults albeit the risk estimates were based on very small number of young patients. Given a small sample size for young epilepsy, further interpretation for the potential effect-modification by age on the sex-specific SMR is rather limited. As nearly all studies found lower mortality in patients in the category of unknown etiology (i.e., idiopathic) than in those patients in the remote symptomatic group including progressive CNS disorders such as brain tumors and neurodegenerative disorders, the observed small difference in sex-specific SMR might be attributable to a higher prevalence of certain progressive CNS disorders in males.[37] Further studies are needed to address whether there is an interactive effects of age and sex on the risk of mortality from epilepsy.

4.3. Cause-specific SMR

Our study findings are generally consistent with previous findings that people with epilepsy are at greater risks of mortality from cerebrovascular disease (CVD),[2,3,6] neoplasm (especially brain cancer),[2,3,6] pneumonia,[2,3] and suicide.[8–10] Nonetheless, our study also noted an increased risk of mortality from certain specific causes such as liver cancer, heart disease, and some injury related causes, which deserved further comments.

One earlier Taiwanese study by Chen et al. of adult patients with epilepsy found that the patients with epilepsy had a 3.5-fold higher risk of death as compared to the general population (SMR: 3.47, 95% CI, 2.46–4.91).[24] Chen et al.'s study also noted that patients with late disease onset (≥40 years) had a 4-fold higher risk of death as compared to those with an earlier onset.[24] This earlier study also observed that one-third of the deaths in patients with age-at-onset between 40 and 59 years died of liver cirrhosis and hepatoma. A higher risk of liver cancer noted in our study could be due to the fact that Hepatitis B virus infection is endemic in Taiwan, and this is closely associated with liver cirrhosis and hepatoma.[24] It is not clear by far whether anticonvulsants might contribute to the hepatotoxicity leading to fatal liver disease in patients with epilepsy.[24] Previous studies suggested that intake of antiepileptic drugs (AEDs) might increase the risk of some malignancies, particularly lung cancer, hepatobiliary and pancreatic tumors. However, our study found no increased SMR for lung cancer in patients with epilepsy in Taiwan.

The patients with epilepsy in our sample experienced a 3-fold higher risk of mortality from heart disease, which is rarely reported in the literature. Nilsson et al. followed more than 9000 patients admitted for epilepsy and observed 4001 deaths in the cohort.[7] The excess mortality rate in the cohort was due to a wide range of causes of death, including diseases of the circulatory system with a SMR similar to ours at 3.1 (95% CI, 3.0–3.3). Benn et al. determined underlying cause-specific mortality for incident unprovoked seizures from Northern Manhattan, New York City, and noted that about 25.0% of the death were attributed to heart, second to the proportion of malignant neoplasm (31.3%).[38] A recent Norwegian study found that both epileptic men and women using carbamazepine (CBZ) had higher total cholesterol, high-density lipoprotein and low-density lipoprotein than controls. They also found that patients with epilepsy recorded less physical activity and lower alcohol use than controls.[39] Further studies are needed to investigate whether medication for treating epilepsy and lifestyle may play certain roles in causing cardiovascular disease in patients with epilepsy.

Apart from a higher risk of suicide death noted in epilepsy, which has been well documented in the literature and has been attributable to a high prevalence of psychiatric comorbidity noted in patients with epilepsy,[10,40] our study also disclosed a higher SMR for motor vehicle traffic accident, accidental falls and accidental drowning and submersion, with substantially high SMRs (8.0–9.0 fold higher) for the later two causes. It has been reported that people with epilepsy are not injured in traffic accidents more often than are those in the general population, and the traffic accidents happened to epilepsy patients tend to be less severe.[7] A recent study reported that an average of 44,027 US drivers died annually as a result of motor vehicle crashes during 1995–1997; however, only 86 (0.2%, range 82–97) of these deaths were associated with seizures in mortality reports.[21] Unlike those previous studies which provided reassurance for the public policy, adopted in some nations but not in all, of permitting patients whose seizures are controlled to drive, our results suggested caution and imposed certain conditions in issuing driver's licenses. Although people with confirm diagnosis of epilepsy are not allowed by law to possess a driver's license in Taiwan, it is believed that many epilepsy patients are still driving in areas where the public transportation is inadequate. Due to limited information, we were not able to further assess how many patients with epilepsy who died of motor vehicle crashes in our sample truly had their epilepsy satisfactorily controlled.

People with epilepsy are thought to be at an increased risk of accidental falls and drowning.[20,41,42] Epilepsy associated handicaps and comorbidity and antiepileptic drugs may cause accidents and injuries by impairing cognitive functions and increasing the patient's susceptibility to suffer from the complications of injuries.[41] Petty et al. investigated chronic AED use and physical contributors to falls risk in treated epilepsy patients, and noted that balance performance is impaired in AED users.[42] In a recent meta-analysis, Bell et al. reported that the risk of drowning in people with epilepsy is raised 15–19-fold compared with the general population.[40] This summary relative risk estimate for drowning is much higher than ours (SMR = 8.0). The lower risk estimates for accidental drowning noted in our study patients might reflect lower prevalence of the above risk factors for impaired cognitive functions in patients with epilepsy from southern Taiwan.

4.4. Strength and limitations

This study has several methodological strengths. First, our study was based on clinical series of patients from a tertiary hospital, which may provide valid data on the diagnosis of epilepsy. Thus, our study was less likely to incur disease misclassification bias. Second, with a sufficient large size, we were able to make age, sex, and cause specific analyses without comprising the statistical power, which also allowed more specific interpretations of the study findings. Third, we linked our study cohort to the national death registry. This way of doing effectively reduced the likelihood of selection bias resulting from patients' loss to follow-up. Despite the above strengths, several limitations should also be stated. First, the study cohort was consisted only of prevalent cases that sought treatment in hospitals, and was unable to include the patients who did not seek treatments or who died soon after disease onset prior to receiving treatment in the cooperation hospital. It is generally agreed that incident cohort differs from the prevalent cohort in many ways. Prevalent cohorts might underestimate short-term mortality because the more serious cases die in the early phase of the disease and are not included in the calculation of deaths over the period of observation.[43] Our study included prevalent cases, which might under-ascertainment of deaths from epilepsy. Second, our study sample was selected from a tertiary hospital, which might have limited the external validity of the results due to the fact that the patients admitted or cared in medical centers are often highly selected.[14,44,45] Third, reliance on death registry in the ascertainment of causes of death may limit our interpretations of study results since the causes of death certified on the death certificate for the deaths of epilepsy patients may not necessarily be epilepsy related.[25] Moreover, because we were not allowed to contact the patients or their family members, or to review patient's medical charts, we were unable to validate the UCOD for the deceased subjects. Despite that, the TDR has been considered accurate and complete,[28] therefore, the potential disease misclassification and under-ascertainment should be minimal; and such disease misclassification is likely to be non-differential, which may lead to under-estimation of effects of epilepsy on mortality, and should not be a valid argument for the significant increased risk of mortality in people with epilepsy observed in this study. Fourth, due to a lack of information on lifestyle, it is not possible for our study to evaluate the roles, if any, of certain risk factors for neoplasm and cerebrovascular disease in causing death in patients with epilepsy. For example, there could be a difference between the smoking habits of people with epilepsy and the general population, and an increased smoking or alcohol intake might be to blame for the increased mortality risk in patients with epilepsy. Fifth, recent studies suggested that the risk of premature death remains significantly elevated at 20–25 years after the index seizure in people with epilepsy,[46] our study was also limited in its length of follow-up. An extension of follow-up period in future studies should be considered to further depict the long-term risk of mortality in people with epilepsy. Last, as an end-point, we used mortality data rather than incidence data. Thus, the concepts of risk and prognosis are mixed.

5. Conclusions

The SMR of all-cause mortality was significantly increased in patients with epilepsy from southern Taiwan. Such increase in risk was especially noticeable in younger patients, who should be the object of aggressive treatments. Effective measures for preventing mortality from injury related causes should be formatted to further reduce the excess of premature deaths for the patients with epilepsy in Taiwan.

References

1. Zielinski JJ. Epilepsy and mortality rate and cause of death. *Epilepsia* 1974;**15**:191–201.
2. Hauser WA, Annegers J, Elveback L. Mortality in patients with epilepsy. *Epilepsia* 1980;**21**:399–412.
3. Cockerell OC, Johnson AL, Sander JW, Hart YM, Goodridge DM, Shorvon SD. Mortality from epilepsy: results from a prospective population based study. *Lancet* 1994;**344**:918–21.
4. Olafsson E, Hauser WA, Gudmundsson G. Long-term survival of people with unprovoked seizures: a population-based study. *Epilepsia* 1998;**39**:89–92.
5. Beghi E, Leone M, Solari A. Mortality in patients with a first unprovoked seizure. *Epilepsia* 2005;**46**:40–2.
6. Lindsten H, Nyström L, Forsgren L. Mortality in an adult cohort with newly diagnosed unprovoked epileptic seizure. A population-based study. *Epilepsia* 2000;**41**:1469–73.
7. Nilsson L, Tomson T, Farahmand BY, Diwan V, Persson PG. Cause-specific mortality in epilepsy: a cohort study of more than 9000 patients once hospitalized for epilepsy. *Epilepsia* 1997;**38**:1062–8.
8. Harris EC, Barraclough B. Suicide as an outcome for mental disorders. A meta-analysis. *Br J Psychiatry* 1997;**170**:205–28.
9. Pompili M, Girardi P, Ruberto A, Tatarelli R. Suicide in the epilepsies: a meta-analytic investigation of 29 cohorts. *Epilepsy Behav* 2005;**7**:305–10.
10. Bell GS, Gaitatzis A, Bell CL, Johnson AL, Sander JW. Suicide in people with epilepsy: how great is the risk? *Epilepsia* 2009;**50**:1933–42.
11. Neligan A, Bell GS, Shorvon SD, Sander JW. Temporal trends in the mortality of people with epilepsy: a review. *Epilepsia* 2010;**51**:2241–6.
12. Jallon P. Mortality in patients with epilepsy. *Curr Opin Neurol* 2004;**17**:141–6.
13. Forsgren L, Hauser WA, Olafsson E, Sander JW, Sillanpää M, Tomson T. Mortality of epilepsy in developed countries: a review. *Epilepsia* 2005;**46**(Suppl. 11):18–27.
14. White SJ, McLean AEM, Howland C. Anticonvulsant drugs and cancer: a cohort study in patients with severe epilepsy. *Lancet* 1979;**2**:458–60.
15. Nashef L, Fish DR, Garner S, Sander JW, Shorvon SD. Sudden death in epilepsy: a study of incidence in a young cohort with epilepsy and learning difficulty. *Epilepsia* 1995;**36**:1187–94.
16. Nashef L, Fish DR, Sander JW, Shorvon SD. Incidence of sudden unexpected death in an adult outpatient cohort with epilepsy at a tertiary referral centre. *J Neurol Neurosurg Psychiatry* 1995;**58**:462–4.
17. Forsgren L, Edvinsson SO, Nyström L, Blomquist HK. Influence of epilepsy on mortality in mental retardation: an epidemiologic study. *Epilepsia* 1996;**37**:956–63.
18. Shackleton DP, Westendorp RG, Trenité DG, Vandenbroucke JP. Mortality in patients with epilepsy: 40 years of follow up in a Dutch cohort study. *J Neurol Neurosurg Psychiatry* 1999;**66**:636–40.
19. Annegers JF, Hauser JF, Shirts SB. Heart disease mortality and morbidity in patients with epilepsy. *Epilepsia* 1984;**25**:699–704.
20. Bell GS, Gaitatzis A, Bell CL, Johnson AL, Sander JW. Drowning in people with epilepsy: how great is the risk? *Neurology* 2008;**71**:578–82.
21. Sheth SG, Krauss G, Krumholz A, Li G. Mortality in epilepsy: driving fatalities vs other causes of death in patients with epilepsy. *Neurology* 2004;**63**:1002–7.
22. Hitiris N, Mohanraj R, Norrie J, Brodie MJ. Mortality in epilepsy. *Epilepsy Behav* 2007;**10**:363–76.
23. Carpio A, Bharucha NE, Jallon P, Beghi E, Campostrini R, Zorzetto S, et al. Mortality of epilepsy in developing countries. *Epilepsia* 2005;**46**(Suppl. 11):28–32.
24. Chen RC, Chang YC, Chen TH, Wu HM, Liou HH. Mortality in adult patients with epilepsy in Taiwan. *Epileptic Disord* 2005;**7**:213–9.
25. Tsai JJ. Mortality of epilepsy from national vital statistics and University epilepsy clinic in Taiwan. *Epilepsia* 2005;**46**(Suppl. 11):8–10.
26. Chen CC, Chen TF, Hwang YC, Wen YR, Chiu YH, Wu CY, et al. Population-based survey on prevalence of adult patients with epilepsy in Taiwan (Keelung community-based integrated screening no. 12). *Epilepsy Res* 2006;**72**:67–74.
27. Commission on Epidemiology and Prognosis, International League against Epilepsy Guidelines for epidemiologic studies on epilepsy. *Epilepsia* 1993;**34**:592–6.
28. Lu TH, Lee MC, Chou MC. Accuracy of cause-of-death coding in Taiwan: types of miscoding and effects on mortality statistics. *Int J Epidemiol* 2000;**29**:336–43.
29. Ulm K. A simple method to calculate the confidence interval of a standardized mortality ratio. *Am J Epidemiol* 1990;**131**:373–5.
30. Dobson AJ, Kuulasmaa K, Eberle E, Scherer J. Confidence intervals for weighted sums of Poisson parameters. *Stat Med* 1991;**10**:457–62.
31. Sillanpää M, Shinnar S. Long-term mortality in childhood-onset epilepsy. *N Engl J Med* 2010;**363**:2522–9.
32. Plioplys S. Depression in children and adolescents with epilepsy. *Epilepsy Behav* 2003;**4**(Suppl. 3):S39–45.
33. Ekinci O, Titus JB, Rodopman AA, Berkem M, Trevathan E. Depression and anxiety in children and adolescents with epilepsy: prevalence, risk factors, and treatment. *Epilepsy Behav* 2009;**14**:8–18.
34. O'Callaghan FJ, Osmond C, Martyn CN. Trends in epilepsy mortality in England and Wales and the United States, 1950–1994. *Am J Epidemiol* 2000;**151**:182–9.
35. Hauser WA, Hesdorffer D. *Epilepsy: frequency, causes and consequences*. New York: Demos Publications; 1990.

36. Brorson LO, Wranne L. Long-term prognosis in childhood epilepsy: survival and seizure prognosis. *Epilepsia* 1987;**28**:324–30.
37. Amirian E, Scheurer ME, Bondy ML. The association between birth order, sibship size and glioma development in adulthood. *Int J Cancer* 2010;**126**:2752–6.
38. Benn EK, Hauser WA, Shih T, Leary L, Bagiella E, Dayan P, et al. Underlying cause of death in incident unprovoked seizures in the urban community of Northern Manhattan, New York City. *Epilepsia* 2009;**50**:2296–300.
39. Svalheim S, Luef G, Rauchenzauner M, Mørkrid L, Gjerstad L, Taubøll E. Cardiovascular risk factors in epilepsy patients taking levetiracetam, carbamazepine or lamotrigine. *Acta Neurol Scand Suppl* 2010;(190):30–3.
40. Bell GS, Mula M, Sander JW. Suicidality in people taking antiepileptic drugs: what is the evidence? *CNS Drugs* 2009;**23**:281–92.
41. Beghi E. Accidents and injuries in patients with epilepsy. *Expert Rev Neurother* 2009;**9**:291–8.
42. Petty SJ, Hill KD, Haber NE, Paton LM, Lawrence KM, Berkovic SF, et al. Balance impairment in chronic antiepileptic drug users: a twin and sibling study. *Epilepsia* 2010;**51**:280–8.
43. Logroscino G, Hesdorffer DC. Methodologic issues in studies of mortality following epilepsy: measures, types of studies, sources of cases, cohort effects, and competing risks. *Epilepsia* 2005;**46**:3–7.
44. Klenerman P, Sander JWAS, Shorvon SD. Mortality in patients with epilepsy: a study of patients in long-term residential care. *J Neurol Neurosurg Psychiatry* 1993;**56**:149–52.
45. Iivanainen M, Lehtinen J. Causes of death in institutionalized epileptics. *Epilepsia* 1979;**20**:485–91.
46. Neligan A, Bell GS, Johnson AL, Goodridge DM, Shorvon SD, Sander JW. The long-term risk of premature mortality in people with epilepsy. *Brain* 2011;**134**(Pt 2):388–95.